(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 914 818 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
12.05.1999 Bulletin 1999/19

(21) Application number: **97927372.9**

(22) Date of filing: **12.06.1997**

(51) Int. Cl.[6]: **A61K 9/20**, A61K 47/10, A61K 47/26, A61J 3/10

(86) International application number:
PCT/JP97/02032

(87) International publication number:
WO 97/47287 (18.12.1997 Gazette 1997/54)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **14.06.1996 JP 153553/96**
25.03.1997 JP 71107/97

(71) Applicant:
KYOWA HAKKO KOGYO CO., Ltd.
Chiyoda-ku, Tokyo 100 (JP)

(72) Inventors:
- **OHTA, Motohiro**
  Sunto-gun, Shizuoka 411 (JP)
- **HAYAKAWA, Eiji**
  Susono-shi, Shizuoka 410-11 (JP)
- **ITO, Kunio**
  Sunto-gun, Shizuoka 411 (JP)
- **TOKUNO, Sanji**
  Tokyo 142 (JP)
- **MORIMOTO, Kiyoshi**
  Mishima-shi, Shizuoka 411 (JP)
- **WATANABE, Yasushi**
  Numazu-shi, Shizuoka 410 (JP)

(74) Representative:
Sajda, Wolf E., Dipl.-Phys.
MEISSNER, BOLTE & PARTNER
Postfach 86 06 24
81633 München (DE)

(54) INTRAORALLY RAPIDLY DISINTEGRABLE TABLET

(57) A tablet comprising sugar alcohol or saccaride having an average particle diameter of not more than 30 µm, an active ingredient, and a disintegrant. It is an intraorally rapidly disintegrable tablet which does not require a special pharmaceutical manufacturing technology and can be simply and easily produced by a normal equipment.

EP 0 914 818 A1

(drug for peripheral nervous system)

[0009]

skeletal muscle relaxant • • • chlorphenesin carbamate, chlormezanone, and so on
autonomic nervous agent • • • valethamate bromide, tofisopam, and so on
antispasmodic • • • afloqualone, and so on

(drug for circulatory organ)

[0010]

cardiac • • • ubidecarenon, aminophylline, etilefrine hydrochloride, and so on
antiarrhythmic agent • • • atenolol, pindolol, and so on
diuretic • • • spironolactone, trichlormethiazide, furosemide, and so on
antihypertensive agent • • • todrazine hydrochloride, nicardipine hydrochloride, hydralazine hydrochloride, and so on
angiotonic • • • dihydroergotamine mesilate and so on
vasodilator • • • benidipine hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, and so on
hyperlipemia • • • clinofibrate, nicomol, and so on
others • • • flunarizine hydrochloride, meclofenoxate hydrochloride, cinnarizine, and so on

(alimesitary tract drug)

[0011]

antidiarrheal drug • • • loperamide hydrochloride, dimeticone, and so on
drug for peptic ulcer • • • azulene, L-glutamine, aceglutamide aluminium, cetraxate hydrochloride, cimetidine, and so on
cholagogue • • • anetholtrithion, chenodeoxycholic acid, and so on
others • • • domperidone, trimebutine maleate, metoclopramide, cisapride and so on

(metabolic drug)

[0012]

vitamin • • • alfacarcidol, tiamine hydrochloride, cobamide, vitaroxin riboflavin butyrate, ascorbic acid, phytonadione, and so on

diabetes mellitus agent • • • glybuzole, tolbutamide, and so on

(antiallergics)

[0013]

antihistamine • • • homochlorcyclizine hydrochloride, clemastine fumarate, chlorpheniramine maleate, and so on
others • • • oxatomide, ketotifen fumarate, azelastin hydrochloride, and so on

(antineoplastics)

[0014]

antimetabolite • • • fluorouracil, tegafur, and so on

(antibiotics)

[0015]

paromomycin sulfate, amoxicillin, cefaclor, cefalexin, acetylspiramycin, minocycline hydrochloride, and so on

[0016] In the present invention, crosspovidone, crosscarmellose sodium, low substituted hydroxypropylcellulose or the like, which are widely used for drugs and food can be used as a disintegrant. At least one kind of disintegrant is used.

[0017] Next, a production method of a tablet according to the present invention will be described hereinafter.

[0018] The tablet of the present invention can be obtained by compressing and tableting after granulating a mixed powdered component comprising sugar alcohol or saccaride having an average particle diameter of not more than 30 μm ground by means of a hammer mill or a jet mill or the like, an active ingredient, and a disintegrant. On the other hand, the tablet of the present invention also can be obtained by compressing and tableting after granulating a mixed powdered component comprising sugar alcohol or saccaride having an average particle diameter of not more than 30 μm ground by means of a hammer mill, a jet mill or the like, an active ingredient, and a disintegrant under the presence of an easily volatile disintegrating adjuvant and thereafter the disintegrant adjuvant is volatilized.

[0019] The amount of sugar alcohol or saccaride is preferably about 60 ~ 95%, more preferably about 80 ~ 95% per one tablet.

[0020] The amount of active ingredient is different depending on the kind and dosage amount of active ingredients, however, 0.01 ~ 30% is preferable, and more preferably 0.01 ~ 10% per one tablet.

[0021] The amount of disintegrant present is preferably about 1 ~ 30mg per dosage, and more preferably 1 ~ 10% per one tablet.

[0022] Easily volatile disintegrating adjuvant is such as sublimative camphor, urethane, urea, ammonium bicarbonate, benzonic acid, or the like, however, camphor is most preferable. The amount of easily volatile disintegrating adjuvant is preferably 1 ~ 20% and more preferably 1 ~ 10% per one tablet.

[0023] A wet granulation method using purified water, ethanol or the like can be preferably used. In the method, for example, granulation can be executed by means of a general granulator such as a fluid-bed granulator, a rotary stirring granulator or an extruding granulator. The granulated material is dried, and mixed with a lubricant, and thereafter compressed into predetermined shape. Binder, sour agent, foaming agent, sweetening agent, flavoring agent, or colorant can be added as additive. As a lubricant, such as magnesium stearate, stearic aid, stearyl alcohol, sucrose ester of fatty acid, talc, light anhydrous silicic acid, or like can be used. Binder is, for example, hydroxypropylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose, partially saponificated polyvinyl alcohol methylcellulose, pullulan or the like. Sour agent is citric acid, malic acid, adipic acid, ascorbic acid, or the like. Foaming agent is sodium bicarbonate, sodium carbonate, calcium carbonate, or the like. Sweetening agent is Aspartame (TM), saccharin, glycyrrhizic acid or the like. Flavoring agent is lemon, orange, pine, mint, menthol or the like. Colorant is yellow iron sesquioxide, red iron sesquioxide, tar color or the like. The amount of lubricant is preferably 0.01 ~ 1% and more preferably 0.01 ~ 0.5% per one tablet.

[0024] Although a method of compression is not limited in the present invention, a rotary tablet machine, a hydraulic press machine or a single punch tableting machine which have high productivity can be more preferably used. When an easily volatile disintegrating adjuvant is used, the tablet is dried by heating after compressing process. As to lubricants, they can be excluded from the powdered mixture in the granulation process, in that occasion it may be previously spread on the surfaces of punches and dies of a tableting machine before compression process. That makes the present invention more effective. Compression pressure of a rotary tablet machine may be preferably more than 300kg.

[0025] The shape of the tablet obtained in the present invention can be pills or other shapes such as a normal R surface tablet, a sugar coated R surface tablet, a tablet with square edges, a tablet with rounded edges, or a tablet with two R surfaces, or the like.

[0026] Further, the tablet may have a divisional line.

Best Mode for Carrying Out the Invention

[0027] The present invention will be concretely explained according to examples and reference examples.

Reference Example 1

[0028] 1890g of D-mannitol (Towa Kasei Co., Ltd. : average particle diameter of about 60 μm) and 100g of crosspovidone (POLYPLASDONE XL-10 : GAF Co., Ltd.) were fed in a fluid-bed granulation dryer (Glatt Co., Ltd. : WSG-type 5), purified water was sprayed, then granulated material was obtained after granulation and drying processes. 10g of magnesium stearate was added and mixed with the granulated material, and they were compressed and tableted by a rotary

tablet machine (Kikusui Seiko Co., Ltd., CLEAN PRESS COLLECT TYPE 12). Tableting conditions were as follows; tablet weight was 200mg, a metal mold was 8mm diameter flat-type, and compression pressure was varied such as 150kg, 300kg, 450kg, 600kg, and 800kg.

Example 1

[0029] D- mannitol (Towa Kasei Co., Ltd. : average particle diameter of about 60 μm) was previously ground by a jet mill (Japan Pneumatic Co., Ltd.:type PJM-1-1.5) and the pulverized D-mannitol with average particle diameter of 20 μm was obtained. 1890g of the pulverized D-mannitol and 100g of crosspovidone (POLYPLASDONE XL-10 : GAF Co., Ltd.) was fed in a fluid-bed granulation dryer (Glatt Co., Ltd. : WSG-type 5), purified water was sprayed, and granulated material was obtained after granulation and drying processes. 10g of magnesium stearate was added and mixed with the granulated material, and they were compressed and tableted by a rotary tablet machine (Kikusui Seiko Co., Ltd., CLEAN PRESS COLLECT TYPE 12). Tableting conditions were the same as the referenc example 1.

Reference Example 2

[0030] 100g of domperidone, antiemetic agent, 1790g of lactose (DMV Co., Ltd. : average particle diameter of about 80 μm) and 100g of crosspovidone (POLYPLASDONE XL-10 : GAF Co., Ltd.) were fed in a fluid-bed granulation dryer (Glatt Co., Ltd. : WSG-type 5), purified water was sprayed, and granulated material was obtained after granulation and drying processes. 10g of magnesium stearate was added and mixed with the granulated material, and they were compressed and tableted by a rotary tablet machine (Kikusui Seiko Co., Ltd., : CLEAN PRESS COLLECT type 12). Tableting conditions were the same as the reference example 1.

Example 2

[0031] Lactose (DMV Co., Ltd. : average particle diameter of about 80 μm) was previously ground by a jet mill (Japan Pneumatic Co., Ltd. : type PJM-1-1.5) and the pulverized lactose having average particle diameter of 15 μm was obtained. 1790g of the pulverized lactose, 100g of domperidone, and 100g of crosspovidone (POLYPLASDONE XL-10: GAF Co., Ltd.) were fed in a fluid-bed granulation dryer (Glatt Co., Ltd.: WSG-type 5), purified water was sprayed, and granulated material was obtained after granulation and drying processes. 10g of magnesium stearate was added and mixed with the granulated material, and they were compressed and tableted by a rotary tablet machine (Kikusui Seiko Co., Ltd., CLEAN PRESS COLLECT TYPE 12). Tableting conditions were the same as the reference example 1.

Example 3

[0032] The granulated material obtained in the example 1 was tableted under the condition that tablet weight was 200mg, compression pressure was 50kg/c m^2, and a little magnesium stearate was coated on a metal mold (8mm diameter flat-type) and dies of a hydraulic press machine (Riken Seiki Co., Ltd.: type P-1B)

Example 4

[0033] 140g of the pulverized D-mannitol used in the example 1, 10g of domperidone, 10g of crosspovidone (POLYPLASDONE XL-10 : GAF Co., Ltd.) and 40g of camphor were mixed in a vinyl bag and tableted under the condition that tablet weight was 200mg, a metal mold diameter was 9mm, a single punch tableting machine (Okada Seiko Co., Ltd.: N-20E type both pressure powder tableting machine) was used, and compression pressure was 1500kg/cm^2. The compressed tablet was dried for 10 minutes at 80 °C under vacuum condition in a vacuum dryer.

[0034] Next, the hardness and disintegrating time of the tablet of the present invention will be described using an experimental example.

Experimental Example

[0035] The hardness and the disintegrating time of the tablet obtained by the examples 1 and 2 and reference examples 1 and 2 were measured. The hardness of the tablet was measured by a tablet destructive strength measuring instrument (Toyama Sangyo Co., Ltd. : TH- 203CP type) The disintegrating time of the tablet was measured in such a way that the tablet was placed on a No.10 wire cloth, water was dropped at a speed of 4ml/min. on the tablet, and the time till the tablet go through the wire cloth was measured. The time was determined as the disintegrating time.

[0036] The result is shown in a Table 1.

Table 1

sample/compression pressure		150kg	300kg	450kg	600kg	800kg
comparison 1	hardness	hard to be tableted	hard to be tableted	hard to be tableted	1.9kgf	2.3kgf
	disintegration	-	-	-	20sec.	22sec.
embodiment 1	hardness	1.9kgf	3.9kgf	5.1kgf	6.2kgf	7.3kgf
	disintegration	10sec.	15sec.	16sec.	19sec.	27sec.
comparison 2	hardness	hard to be tableted	hard to be tableted	hard to be tableted	1.5kgf	2.1kgf
	disintegration	-	-	-	18sec.	21sec.
embodiment 2	hardness	1.6kgf	4.0kgf	4.9kgf	5.8kgf	6.5kgf
	disintegration	10sec.	16sec.	20sec.	25sec.	29sec.

[0037] In reference examples 1 and 2, tableting was hard till 450kg compression pressure and tableting was made possible at around 600kg. However, the hardness of the tablet was not enough. In examples 1 and 2, enough tablet hardness could be obtained at more than 300kg compression pressure and the disintegrating time was very fast. When the tablet produced at 450kg compression pressure according to the example 1 was dosed, the tablet was disintegrated within 10 seconds in an oral cavity.

[0038] The tablets obtained by the examples 3 and 4 were also measured of its hardness and disintegrating time in the same way. The tablets obtained by the example 3 had enough hardness of about 6.5kgf and its disintegrating time was about 10 seconds. The hardness of the tablet of the example 4 was about 4kgf and its disintegrating time was about 2 seconds, which was very fast.

Industrial Applicability

[0039] According to the present invention, a tablet rapidly disintegrable in an oral cavity can be provided.

Claims

1. A tablet comprising;

   sugar alcohol or saccaride each having an average particle diameter of not more than 30 μm,
   an active ingredient, and
   a disintegrant.

2. The tablet as set forth in claim 1, wherein the tablet contains disintegrant of 1 to 30mg for one dosage.

3. The tablet as set forth in claim 1 or 2,wherein said sugar alcohol is D-mannitol.

4. The tablet as set forth in claim 1 or 2, wherein said saccaride is lactose.

5. The tablet as set forth in claim 1, 2, 3 or 4, wherein said disintegrant is crosspovidone, crosscarmellose sodium, or low substituted hydroxypropycellulose.

6. A production method of a tablet characterized by compressing powdered mixture which comprises sugar alcohol or saccaride each having an average particle diameter of not more than 30 μm, an active ingredient, and a disintegrant.

7. The production method of a tablet as set forth in claim 6, wherein a tableting machine is employed in compressing process of the method which is provided with punches and dies previously spread with lubricants.

8. The production method of a tablet as set forth in claim 6, wherein powdered mixture which comprises sugar alcohol or saccaride each having an disintegrant is compressed into the tablet under the existence of a readily volatilizable disintegrating adjuvant and thereafter the disintegrant adjuvant is volatilized from the compressed tablet.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/02032

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K9/20, A61K47/10, 47/26, A61J3/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K9/20, A61K47/10, 47/26, A61J3/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 2-172918, A (EGIS Cyogyszerguar), July 4, 1990 (04. 07. 90), Claim & GB, 2224207, A1 & FR, 2638357, A1 & DE, 3936112, A1	1-3, 5-7
A	JP, 49-69819, A (Boehringer Mannheim GmbH.), July 5, 1974 (05. 07. 74) & DE, 2246013, A1 & FR, 2199973, A1 & US, 3885026, A	8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
September 4, 1997 (04. 09. 97)	September 17, 1997 (17. 09. 97)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)